Appl. No. : 09/494,751
Applicant : Smith
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Title : ASSAYS FOR TSH RECEPTOR AUTOANTIBODIES

TC/A.U. : 1641
Examiner : P. Do

Docket No. : 7500.393USWO

Commissioner for Patents
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DECLARATION OF BERNARD REES SMITH

I, Bernard Rees Smith, am the Managing Director of RSR Limited and have extensive knowledge in the area of monoclonal antibody production. I am a co-inventor of US Patent Application Serial Number 09/494,751. I have read and understand the Office Action dated November 18, 2002.

In Example 1 the specification describes the preparation of cDNA clones for the full length porcine thyroid stimulating hormone receptor (TSHR). RNA was cloned from porcine thyroid tissue and mRNA was then purified. This mRNA was employed to synthesize a cDNA library, from which full length porcine TSHR were obtained and fully sequenced. These techniques were well known in the art at the time the invention was made.

Example 2 describes transfecting the full-length TSHR into CHO cells to make a stable cell line expressing recombinant TSHR. Example 3 describes the preparation of detergent solubilized recombinant porcine TSHR expressed by the stable cell line of Example 2. Expressing the recombinant TSHR as a fusion protein with glutathione S-transferase (GST) is described in Example 4. The last 160 amino acids of the TSH receptor encoded by cDNA base pairs 1809 to 2295 was employed in the fusion protein because it represents a region of the TSH receptor that is almost entirely intracellular and as such is unlikely to interact with TSH receptor autoantibodies present in the circulation.

The preparation of monoclonal antibodies is taught in Example 5. These techniques were also well known in the art at the time the invention was made.

The procedures described in Examples 1 - 5 have been repeated at RSR Limited and RSR Limited have prepared and characterized a second monoclonal antibody, 8B7. Like the 4E31 antibody described in the specification, 8B7 binds to an epitope region of the TSH receptor distinct from an epitope region recognized by autoantibodies to the TSH receptor.

The attached Table 1 and Table 2 provide results of assays performed with whole antibody 8B7 and 8B7 Fab_2 fragments, respectively. The assays were performed as described in Example 6, with the modification that the antibody 8B7 was immobilized on ELISA plates instead of magnetic beads, and the TSH was labeled with biotin instead of ^{125}I. Streptavidin-peroxidase and the peroxidase substrate TMB were used to measure the biotin.

As shown in Tables 1 and 2, monoclonal antibody 8B7 can be used to immobilize TSHR to a solid phase while still allowing either TSH-biotin or TSHR autoantibodies to bind the immobilized TSHR. Therefore, antibody 8B7 binds TSHR at an epitope distinct from the epitope bound by TSH and autoantibodies to TSHR.

Based on the disclosure in the specification and the techniques well-known to one of skill in the art at the time the invention was made, one would be able to produce additional monoclonal antibodies with the characteristic of binding TSHR at an epitope distinct from the epitope bound by TSH and autoantibodies to TSHR. No undue experimentation would be required to make the antibodies of the invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issued thereon.

2nd May 2003
Date

Bernard Rees Smith